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CNS Late Effects After ALL Therapy in Childhood. Part II: Conventional EEG Recordings in Asymptomatic Long-Term Survivors of Childhood ALL—An Evaluation of the Interferences Between Neurophysiology, Neurology, Psychology, and CNS Morphology

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Monitoring of therapy-related late effects after acute lymphoblastic leukemia (ALL) therapy in childhood has become an increasingly important area in posttherapeutic patient surveillance. The usefulness of conventional electroencephalographic (EEG) investigations as part of these attempts is controversially discussed. However, EEG recordings have become a popular approach for judgement on the functional integrity of the central nervous system in this subject group. The present report focuses on this problem and discusses the question whether and to what extent conventional EEG recordings were correlated with further measures of central nervous system (CNS) integrity and therapeutic differences.

EEGs were recorded in 110 subjects, asymptomatic long-term survivors of ALL in childhood, during a large retrospective multicenter study evaluating CNS late sequelae following antileukemic therapy in Germany and Austria. EEG findings were correlated with demographic data, illness- and treatment-related parameters, as well as with data on the morphological, neurological and psychological status of the participating subjects.

At the time of follow-up the EEG was abnormal in 47 cases (42.7%). The most frequent EEG abnormalities observed were disturbances of the background activity (n = 45, 95.8%), followed by hypersynchrone activities (n = 10, 21.3%) and interhemispheric differences/focal slowings (n = 6, 12.8%). With exception of age at diagnosis, none of the observed EEG abnormalities showed a correlation with any of the aforementioned illness- or treatment-related parameters. Eighty percent of the observed EEG abnormalities were found in children younger than 5 years at diagnosis. Children less than 2 years of age as well as those above 5 years at onset of disease showed a significantly reduced prevalence of EEG disturbances compared to subjects between 2 and 5 years at diagnosis. Neither the degree of illness nor therapy-specific differences showed any relationship to EEG outcome. There was no specific EEG finding for a specific morphological substrate, neurological or psychological deficiency and vice versa. Overall, there was no beneficial effect of routine EEG testing in children following therapy for ALL.

According to our data, the evaluation of conventional EEG recordings of otherwise asymptomatic ALL long-term survivors is not a very helpful measure for predicting the degree of behavioral deficiencies, neurological disturbances, or morphological CNS abnormalities, which may be present or will develop in this special subject group. Med. Pediatr. Oncol. 29: 121–131, 1997.

Key words: EEG; acute lymphoblastic leukemia in childhood; CNS late sequelae; ALL long-term survivors

INTRODUCTION

Due to the improvement in treatment of the acute lymphoblastic leukemia (ALL) during the past 25 years, about 70% of all children newly diagnosed with this neoplastic disease now survive in complete continuous remission for more than 5 years and most of them remain free of disease for the rest of their lives [1]. With prolonged survival more attention is focused on the side effects of these treatment efforts for long-term disease control [2,3]. Especially adverse effects of central nervous system (CNS) prophylaxis on CNS integrity of children surviving ALL, whether related to cranial irradiation or to chemical neurotoxicity, are a specific concern

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[4]. Promoted by its importance for the surveillance of cerebral seizures and related CNS disturbances, the investigation of the brain electrical activity by means of neurophysiological techniques developed into one of the favoured instruments for functional CNS screening procedures in clinical practice. For several years, conventional EEG recordings have been widely used for the evaluation of patients with leukemia to assess either the prognosis [5], acute neurotoxic side effects of anticancer treatment [6, 7], or to assist in the differential diagnosis of CNS involvement [8,9]. However, its usefulness has not been established for any of these purposes and no conformity exists either about its sensitivity or specificity, or its predictivity for further treatment-related abnormalities in CNS morphology and function.

In 1992, we initiated a retrospective multicenter study in Germany and Austria to evaluate CNS late effects after ALL therapy in childhood [10]. One aim of this study was to define the value of the EEG as a follow-up measure for routinely performed screening procedures during posttherapeutic patient surveillance, particularly its predictive value on the morphological, neurological and psychological status. This report focuses on the neurophysiological EEG data obtained during this study, whereas results of the other CNS features studied are presented in a summarised fashion to highlight the existence of interferences between them.

MATERIALS AND METHODS

Subjects

Based on information provided by the National German Register for Childhood Cancer, long-term survivors of acute lymphoblastic leukemia in childhood, who fell ill between 1981 and 1986, were identified and invited in writing to participate in a follow-up study evaluating CNS late sequelae of ALL therapy. Eligibility requirements for entry into the follow-up trial included: (1) a diagnosis of acute lymphoblastic leukemia without CNS involvement, scored as (2) standard/low or intermediate risk (i.e., risk factor <1.7); (3) standardised ALL therapy according to the treatment protocols BFM-81 or BFM-83, as recommended by the German BFM study guidelines [10–12]; (4) treatment completion without CNS complications on the aforementioned protocols; (5) first continuous complete remission (1CCR) and freedom from leukemic relapse for more than 4 years after establishment of diagnosis and initiation of therapy; (6) an age equal to or greater than 6 years at follow-up assessment, and (7) the attendance of a German school. Exclusion criteria were: (1) further neoplasms; (2) leukemic CNS involvement; (3) evidence of a meningeal or encephalitic infection; (4) obvious neurologic handicaps or psychological deterioration; (5) constitutional numeric or structural chromosomal aberrations, and (6) a history of perinatal acquired brain damage. Two hundred and fifty subjects met these criteria and their families were contacted by letter, outlining the purposes of the study and requesting their participation. Between June 1992 and May 1994, a total of 163 ALL long-term survivors agreed to participate, entered our study and passed through an extensive standardised follow-up protocol consisting of clinical, neurophysiological, psychological, and neuroradiological investigations. An evaluation of demographic and illness-related data revealed no significant differences between this group of participants and the originally invited subject group. The whole follow-up trial was carried out according to the Declaration of Helsinki (1975, revised in 1983) and the study design was approved by the Medical Ethics Committee of the University of Erlangen (Erlangen, Germany). Informed consent was obtained from the parents in case subjects were younger than 18 years, respectively from the participants themselves if they were of full age. Of this initial sample, 15 participants (9.2%) had to be excluded from further analyses due to violations of study inclusion criteria. Furthermore 38 cases (i.e., 25.7% of the remaining 148 subjects) were excluded because their follow-up investigation was not performed according to the recommendations of the CNS late sequelae study group: in 24 subjects (16.2%) no neuromorphological investigation was performed; in 10 cases (6.8%) no EEG recordings were obtained, and in four further subjects (2.7%), neither neurological nor psychological data were available. Our series comprised 110 subjects whose data were completely available until the end of December 1994. Statistical comparisons between this final population and the remaining group of 53 study participants revealed no significant differences, either with respect to illness- or treatment-related data or to the available follow-up data.

Disregarding minor differences between protocol branches and their recommendations for CNS prophylaxis, our study population consisted of three distinct treatment groups: (1) those who did not receive cranial irradiation to the central nervous system (methotrexate group [MTX]; BFM-81/SR-B, BFM-83/SR-L; n = 34); (2) those who received cranial irradiation after chemotherapy (methotrexate-radiotherapy group [MTXRT]; BFM-83/SR-H2, BFM-83/MR; n = 38); and (3) those who received CNS irradiation prior to or during intrathecal chemotherapy (radiotherapy-methotrexate group [RTMTX]; BFM-81/SR-A, BFM-81/MR); n = 38). Relevant data with respect to initial clinical features, illness and treatment parameters of the total sample of participating subjects and all three treatment groups are summarised in Table I. Ages ranged from 7.98 to 27.81 years (mean 14.85, S.D. 4.51). Age at diagnosis ranged from 0.32 to 16.07 years (mean 5.88, S.D. 4.08). The mean follow-up interval for all participants was 7.19 ± 1.78 years (ranging from 4.45 to 10.55 years); 52.7% of the participating subjects were female. Statistical compari-

TABLE I. Demographic Characteristics, Clinical/Laboratory Data, and Treatment Parameters*

	Overall	Treatment groups			Statistics (F; df; *P*)[a]
		MTX	MTXRT	RTMTX	
Demographic data					
No.	110	34 (30.9%)	38 (34.5%)	38 (34.5%)	
Age at diagnosis (yrs.)	5.88 ± 4.08	6.65 ± 4.49	5.36 ± 3.73	5.71 ± 4.02	0.95; 2; 0.3893
Age at assessment (yrs.)	14.85 ± 4.51	15.54 ± 5.05	12.89 ± 3.69	16.20 ± 4.16	6.02; 2; 0.0028
Posttherapeutic Interval (yrs.)	7.19 ± 1.78	7.07 ± 1.74	5.73 ± 1.0	8.72 ± 1.03	50.84; 2; 0.0001
Male to female ratio	52/58	15/19	19/19	18/20	0.25; 2; 0.8828
Laboratory/clinical data					
Hb (mg/dl)	7.81 ± 2.59	7.01 ± 2.14	8.25 ± 2.64	8.19 ± 2.84	2.31; 2; 0.1052
WBC (cell/μl)	21727.3 ± 31899.5	6948.9 ± 9116.3	28562.0 ± 39759.3	28115.3 ± 32437.9	5.74; 2; 0.0043
Blasts (%)	44.3 ± 32.2	26.74 ± 28.52	53.37 ± 29.82	51.03 ± 31.93	8.42; 2; 0.0004
Blasts (cell/μl)	15879.8 ± 28872.8	3581.8 ± 9037.6	21128.9 ± 34973.0	21634.2 ± 30961.5	4.78; 2; 0.0103
PC (cell/μl)	73891.3 ± 73211.3	84774.2 ± 83663.5	67437.5 ± 59957.5	69379.3 ± 75764.4	0.52; 2; 0.5985
Liver (cm)	3.33 ± 2.53	1.97 ± 2.06	4.02 ± 2.54	3.9 ± 2.47	7.44; 2; 0.0011
Spleen (cm)	2.42 ± 2.67	0.55 ± 1.06	3.39 ± 2.92	3.16 ± 2.58	14.22; 2; <0.0001
Risk factor	0.97 ± 0.38	0.64 ± 0.24	1.09 ± 0.38	1.12 ± 0.31	24.19; 2; <0.0001
Morphology					
FAB 1 (%)	63.2	75.0	52.9	65.0	
2 (%)	18.4	16.7	11.8	25.0	5.53; 4; 0.2371
1–2 (%)	18.4	8.3	35.3	10.0	
Treatment parameters[b]					
Radiotherapy (%)	69.1	0	100	100	
Mean total dose (Gy)	11.71 ± 8.18	—	16.84 ± 2.25	17.52 ± 1.31	2.63; 1; 0.1093
Mean dose/fraction (Gy)	1.16 ± 0.94	—	1.89 ± 0.46	1.71 ± 0.45	2.49; 1; 0.1194
Cumulative energy (MV)	1.86 ± 2.39	—	3.13 ± 1.59	3.65 ± 2.96	0.54; 1; 0.4678
Cumulative MTX ith. (mg)	80.72 ± 21.72	80.82 ± 17.07	93.32 ± 25.95	67.71 ± 10.73	16.86; 2; <0.0001
Cumulative MTX iv. (mg/m^2)	1295.5 ± 956.1	2000 ± 0	1960.53 ± 243.33	—	0.89; 1; 0.3478
Duration (months)	21.72 ± 2.91	21.88 ± 2.91	21.97 ± 2.83	21.32 ± 3.02	0.55; 2; 0.5765

*Abbreviations: MTX, nonirradiated subjects (methotrexate group); MTXRT, study participants who received cranial irradiation after methotrexate (methotrexate-radiotherapy group); RTMTX, ALL long-term survivors who received CNS irradiation prior to or during methotrexate (radiotherapy-methotrexate group); Gy, gray; MTX, methotrexate; ith., intrathecal application; iv., intravenous application; WBC, white blood cell count; PC, platelet count; FAB, French-American-British classification.

[a]Statistics shown in the right column of this table indicate: F/Chi^2-scores (F/C^2) dependent on the test procedure used (F: ANOVA test value, C^2: Chi-square test), degrees of freedom (df), and related *P*-values (*P*).

[b]With the exception of the variables ''Mean total dose,'' ''Mean dose/fraction,'' ''Cumulative energy,'' and ''Cumulative MTX'' in which two-group analyses were calculated, all remaining test procedures were performed between all three study groups.

sons across variables revealed significant differences between the treatment groups with regard to time since establishment of diagnosis, age at assessment and leukemic cell mass. These differences are mainly due to the fact that the segregation into different antileukemic study branches is based on these clinical and laboratory parameters. The question if and to what extent these differences are responsible for neurophysiological abnormalities will be addressed later in this paper.

Neurophysiology

Conventional EEG recordings were performed according to the recommendations of the American Electroencephalographic Society (AEEGS). Twelve channel recordings were taken in semi-darkened, sound-attenuated and electrically shielded rooms. Electrodes were applied to the 10–20 system [13]. Four montages, longitudinal and transverse bipolar, ipsilateral ear and vertex referential, were used for visual analysis. Each record included ~20 minutes registration at rest, with periods with eyes closed and eyes opened, as well as activation phases with intermittent photic stimulation (1–25 cps), and hyperventilation for ~3 minutes plus ~2 minutes follow-up. Visual evaluation of the paper-written EEG recordings was done according to standard principles by one experienced senior clinical neurophysiologist (R.K.) without further information about the subjects' history. Based on data from previous studies about the bioelectrical variability of children suffering from ALL, a structured EEG scoring system was used in which the following EEG criteria had to be accurately specified: (1) background activity: (a) normal, (b) norm-variant, (c) slight, (d) moderate, or (e) severe disturbed; (2) side differences/focal slowings: (a) none, (b) right hemispheric, (c) left hemispheric; and (3) hypersynchrone activities (HSA): (a) none, (b) paroxysmal activ-

ity of focal origin, (c) primary generalized HSA, (d) abnormal rhythms. To facilitate statistical comparisons, EEGs were scored as abnormal if they presented significant bioelectrical deviations (slight, moderate or severe disturbances of the EEG background activity [1c–e], significant interhemispheric differences or focal slowings [2b–c], or any hypersynchrone activity [3b–d]), whereas normal EEGs and those with minor deviations of the background activity (1a–b), which are frequently seen in healthy volunteers, were summed together and scored as normal.

Neuroradiology

In all study participants, cranial CT/MRI scans were performed during this follow-up assessment and offered the opportunity to correlate neurophysiological abnormalities with morphological CNS disturbances. CT/MRI scans were performed in a standardised fashion using axial 4 / 8 mm slices below / above the cerebellar tentorium and a Gantry angulation of −20° in relation to the meato-orbital line to prevent ocular irradiation in case of CT investigations. All scans were interpreted by one experienced senior neuroradiologist (W.J.H.) who had no prior information about the individual histories of the presented cases. On the basis of the results of concurrently performed neuroradiological studies in ALL long-term survivors [14–16] scanograms were evaluated with regard to the presence of: (1) ventricular enlargement and/or widenings of the subarachnoidal space, findings believed to indicate cerebral atrophy; (2) white matter signal abnormalities, suggestive for leukoencephalopathy; and (3) intracerebral calcifications as indicators for calcified focal brain necrosis. CT/MRI scans were classified as normal if they showed no evidence of any of these findings and no further morphological abnormality.

Neurology

To reveal the prevalence and the extent of soft neurologic signs in our study population, we performed a neurological examination according to the standardised methods recommended by B.C.L. Touwen [17]. This examination originally was developed for children with minor cerebral dysfunction, consists of a total of 62 items, divided into 10 categories. With exception of the evaluation of the visual system (part 10 of the Touwen examination) all categories were evaluated: (1) sensorimotor apparatus; (2) posture; (3) balance of the trunk; (4) coordination of the extremities; (5) fine manipulations; (6) dyskinesia; (7) gross motor function; (8) quality of motility; and (9) associated movements. To reduce the inter-rater test variability and to impart a definite amount of experience to each assessor, all paediatricians involved in this project underwent a special training procedure. As a consequence of these efforts, we were able to achieve good reliability scores as well as small inter-rater variabilities. With regard to reports which proclaimed the lack of sensitivity of the Touwen examination for scientific purposes, we calculated neurological profiles across the evaluated categories rather than strict categorical classifications [18]. The evaluation of the examination protocols was blinded, done by the trainee (K.B.-J.) who instructed the assessors in the use of this examination tool.

Psychology

The psychological battery used in this study was designed to assess a variety of functional skills known to be frequently impaired in children surviving ALL, and included measures of general intelligence, concentration, vigilance, perseverance, short-term memory, psychomotor speed, perception and behaviour [19,20]. Test procedures used for this purpose included the German versions of: (1) Wechsler Intelligence Scale for Children-Revised (WISC-R), respectively, the Wechsler Adult Intelligence Scale-Revised (WAIS-R) dependent upon the subjects age at the time of testing; (2) the Culture Fair Test (CFT); (3) the ''d2'' concentration and attention test (d2), and (4) the Recurring Figures Test (RFT). Supplementary information was obtained: (1) from the parents who were asked to complete a standardised questionnaire about the behaviour of their child (Child Behaviour Check List, CBCL), and (2) from a structured interview about medical history, social background and school performance. All psychological examinations were given by trained psychometricians and evaluated by one well experienced psychologist (W.M.) blinded for the subjects' medical history. Test results and intelligence quotient (IQ) values were derived in a conventional manner from the test-specific norms, converted to age-related standards and expressed as percentage scores. Subtest scores obtained for the Wechsler scales were combined to give the following conventional measures: (1) verbal IQ (VIQ), consisting of the subtest information, comprehension, arithmetics, similarities, vocabulary and digit span; (2) performance IQ (PIQ), consisting of the subtest coding, picture completion, picture arrangement, block design and object assembly; and (3) the full-scale IQ (FSIQ), based on all WISC-R/WAIS-R subtests. In addition, three further measures were derived which reflect the main factors of ability defined by Kaufman: (1) verbal comprehension (VC), dependent on subtest similarities and vocabulary; (2) perceptual organisation (PO), calculated from block design and object assembly subtests; and (3) the freedom from distractibility (FD), based on subtest digit span and coding.

Performance

All participants were evaluated in the follow-up departments of the hospitals where they once were treated for leukemia. To prevent an excessive burden caused by the complex and huge battery of investigations necessary

to establish subclinical CNS late sequelae, the assessment was performed according to a standardised time table. The sequence of the study topics was composed to minimise interrelated influences (caused by the test arrangements itself, or by subject-related factors like fatigue or anxiety) and to enhance its practicability for participating subjects. Despite a 2-day follow-up procedure, most evaluations were conducted on an outpatient basis. All involved physicians, psychologists and social care workers were well-trained specialists and experienced in the care of childhood cancer patients. A central review system was established to control for accuracy of coding, performance of the follow-up items and to monitor discrepancies in test results across the participating study sites. To prevent assessor-related differences in test interpretations, data of distinct subspecialties were separately evaluated by one experienced central investigator according to recommendations given by the CNS late sequelae study group. Assessors had no knowledge or information about the performance of the participants in other outcome measures and were unaware of illness and therapy-specific differences between the individuals studied.

Statistical Analysis

For statistical purposes parametric and nonparametric methods were applied according to the nature of the underlying data. The chi-square test was used to evaluate the relationship between pairs of categorial variables and continuous variables assigned to categories. In instances in which there were too few patients for a chi-square analysis, Fisher's exact test was used. One-way analyses of variance (ANOVA) were used to identify differences in continuous variables between groups. To minimise inferential errors associated with the application of excessive univariate test procedures, multivariate ANOVA analyses (MANOVA) were used to compare groups on the basis of more than one outcome measure. All statistics were calculated using the appropriate procedures of the Superior Performing Software System for Windows (SPSS-WIN), Version 5.02 [21].

RESULTS

Overall EEG analysis revealed bioelectrical parameters within normal limits in 63 (57.3%) and disturbed EEG recordings in 47 subjects (42.7%), those being mainly diffuse disturbances of the EEG background activity (32 cases, 68.1%); two participants (4.3%) presented paroxysmal discharges; five cases (10.6%) background disturbances combined with interhemispheric differences/focal slowings (four right hemispheric, one left hemispheric); in 7 subjects (14.9%) the recordings revealed EEG background disturbances combined with paroxysmal activities, and in one subject EEG traces showed disturbances of all three scoring categories. Overall alterations of the background activity were the most frequently observed type of EEG abnormality (n = 45, 95.8%), followed by hypersynchrone discharges (n = 10, 21.3%) and interhemispheric differences/focal slowings (n = 6, 12.8%). Comparisons of the data available within the group of subjects with abnormal EEG recordings showed a homogeneous spectrum of parameters without evidence of treatment- or illness-related influences on distinct EEG disturbances. Based on this analysis, we compared subjects with significant EEG abnormalities with those showing nonpathologic EEG findings. Demographic characteristics, clinical data and treatment parameters of these two groups are presented in Tables II and III. There were no significant differences to observed in terms of illness- and treatment-related parameters. The only factor independently associated with an abnormal EEG outcome was age at diagnosis. As shown in Figure 1, the rate of EEG abnormalities depends primarily on the age when the subject fell ill: more than 76.6% (n = 36) of the abnormal EEGs were seen in children between 2 and 5 years at diagnosis, compared with 8.5% (n = 4) in children younger than 24 months; 8.5% (n = 4) in those 6–8 years of age; and 6.4/4.3% (n = 3/2) in children aged 9–12 and 13–16 years, respectively. Prevalence analyses of abnormal EEG recordings in different age groups revealed highly significant differences (F: 39.33, df: 4, $P < 0.0001$): highest prevalence rates were found for subjects aged 2 to 5 years at diagnosis (n = 34/61, 55.7%), whereas younger (below 24 months: n = 4/11, 36.3%) as well as older ones (6–8 years: n = 4/16, 25%; 9–12 years: n = 3/10, 30%; older than 12 years: n = 2/12, 16.7%) had a substantially lower risk of neurophysiological disturbances.

Data of the psychological test battery are shown in Table IV. Consistent with findings reported in previous studies, our sample of ALL long-term survivors scored higher on most of the performed tests of intelligence than the general population. In general, subjects with EEG abnormalities tended to have a lower score on most of the assessed test items than those with normal EEG recordings, but ANOVA analyses failed to reach the conventionally accepted level of significance, and calculations of the predictive value of the EEG outcome on the outcome in the performed IQ tests did not result in scores superior to classifications obtained by chance (see Table V). However, multivariate analysis performed on the WAIS-R/WISC-R IQ subtests revealed threshold significant differences ($P = 0.048$) between both groups, suggesting a correlation between bioelectrical disturbances and deficiencies in cognitive skills. Features of that relationship are shown in Figure 2, which presents data of the psychological outcome and their relationship to the different types of EEG abnormality. As shown in the left panel of this figure, subjects with normal or normvariant

TABLE II. Demographic Characteristics and Clinical/Laboratory Data for Both EEG Outcome Groups*

	EEG outcome		Statistics
	Normal	Disturbed	(F; df; *P*)
Demographic data			
Frequency	63 (57.3%)	47 (42.7%)	
Age at diagnosis (yrs.)	6.77 ± 4.43	4.68 ± 3.22	**7.56; 1; 0.0071**
Posttherapeutic Interval (yrs.)	7.36 ± 1.89	6.96 ± 1.62	1.35; 1; 0.2482
Male to female ratio	30/33	22/25	0.01; 1; 0.9329
Laboratory data			
Hb (mg/dl)	8.40 ± 2.79	8.03 ± 2.07	0.49; 1; 0.4877
WBC (cells/μl)[a]	27629.6 ± 37706.5	13815.6 ± 19576.3	5.25; 1; 0.0242
Blasts (%)	48.37 ± 33.26	38.91 ± 30.15	2.35; 1; 0.1281
Blasts (cell/μl)	21203.8 ± 34331.7	8743.4 ± 17200.9	5.21; 1; 0.0245
PC (cells/μl)	71830.2 ± 69518.6	76692.3 ± 78792.3	0.09; 1; 0.7548
Clinical data			
Liver (cm)	3.19 ± 2.48	3.52 ± 2.61	0.41; 1; 0.5213
Spleen (cm)	2.47 ± 2.72	2.35 ± 2.66	0.04; 1; 0.8346
Risk factor	0.99 ± 0.41	0.93 ± 0.35	0.84; 1; 0.3606
Morphology			
FAB 1 (%)	60.0	68.4	
FAB 2 (%)	23.3	10.5	1.29; 2 (C^2); 0.5244
FAB 1–2 (%)	16.7	21.1	

*Abbreviations: Hb, haemoglobin; WBC, white blood cell count; PC, platelet count.
[a]Subjects with disturbed EEG recordings had significantly lower WBCs and leukemic blast counts at onset of disease, but with exception of age at diagnosis and initiation of therapy, none of the illness-related parameters shown in this table affects EEG outcome.

TABLE III. Treatment Characteristics for Cases With Normal and Abnormal EEG Recordings*

	EEG outcome		Statistics
	Normal	Disturbed	(F; df; *P*)
Study branch			
MTX	17 (27.0%)	17 (36.2%)	
MTXRT	22 (34.9%)	16 (34.0%)	1.28; 2; 0.5276
RTMTX	24 (38.1%)	14 (29.8%)	
Treatment parameters			
Radiotherapy (%)	73.0	63.8	1.06; 1; 0.3024
Mean total dose (Gy)	12.68 ± 7.88	10.79 ± 8.41	1.47; 1; 0.2278
Mean dose/fraction (Gy)	1.22 ± 0.95	1.08 ± 0.94	0.58; 1; 0.4495
Cumulative energy	2.27 ± 2.75	1.35 ± 1.76	2.82; 1; 0.0971
Cumulative MTX ith. (mg)	78.57 ± 21.83	83.67 ± 21.46	1.47; 1; 0.2275
Cumulative MTX iv. (mg/m^2)	1238.1 ± 979.1	1372.3 ± 929.4	0.53; 1; 0.4689
Duration (months)	21.82 ± 2.88	21.57 ± 2.98	0.19; 1; 0.6617

*Abbreviations as in Table I. Similar to our data shown in Table II, none of the applied therapy strategies showed a correlation with EEG outcome.

background activities showed overall IQ percentile values of 59.4 ± 10.7%, whereas subjects with slightly disturbed EEG background parameters scored at 48.6 ± 12.3 and those with moderate background abnormalities at 33.7 ± 24.1. Comparisons between the IQ measures in subjects with right or left hemispheric amplitude differences or focal slowings (Fig. 2, middle panel) revealed that disturbances of left hemispheric origin were accompanied by clearly impaired cognitive skills: one subject with this EEG abnormality reached mean IQ scores of 42.4 ± 26.7. In contrast, subjects without interhemispheric differences (52.9 ± 12.8) as well as cases with right hemispheric disturbances (54.2 ± 19.7) showed higher overall scores on the obtained IQ measures. Simi-

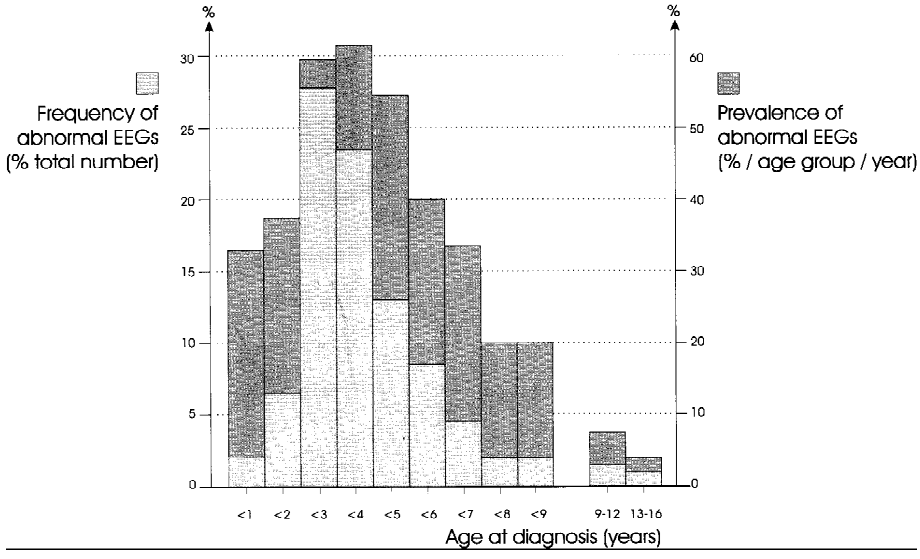

Fig. 1. Distribution of the observed EEG abnormalities in relation to the age at establishment of diagnosis. Clustered bars represent percentage scores of the total amount of abnormal EEG recordings (light grey, scores scaled on the left y-axis) and the observed prevalence (dark grey, scaled on the right y-axis).

lar to these observations of IQ outcome and its dependency from EEG background disturbances and interhemispheric differences, focal or generalised paroxysmal activities without clinical correlates of cerebral seizures (Fig. 2, right panel) seem to exercise no relevant influence on cognitive skills: cases without any signs of hypersynchrone activities (52.7 ± 4.2) did not score substantially better than those with electrophysiologically proven hypersynchrone activities of focal or generalised origin (53.8 ± 15.5, 52.6 ± 19.2). However, the continuous presence of pathological hypersynchronised rhythms in EEG recordings was correlated with lower IQ scores (34.4 ± 8.4) compared with temporally limited focal or generalised hypersynchrone activities. Analyses of the relationship between EEG outcome and further non-IQ-related psychometric variables were unproductive (Table V). EEG outcome groups showed no differences with regard to pathological patterns of behaviour, developmental deficiencies or impaired concentration abilities (Table VI). Furthermore, both EEG outcome groups showed no differences with regard to loss of power in performances at school or at work.

Neurological profiles for both EEG ouctome groups were comparable. Overall mean scores for our study population (50.1 ± 5.38) are consistently below the expected normal range, showing threshold differences between both groups with overall scores of 50.9 ± 5.4 for subjects with inconspicuous EEGs and scores of 48.8 ± 6.7 for cases with abnormal EEG findings (F: 3.46, df: 1, *P:* 0.07). For the whole sample, mean differences to normality were strongest among the categories posture (−4.4), sensorimotor apparatus (−1.62), extremity coordination (−1.26), gross motor function (−1.14), and fine motor skills (−1.05). Between EEG groups, ANOVA reveals significant differences in the categories fine manipulation (F: 4.05, $P < 0.05$), dyskinesia (F: 4.14, p: 0.04), and gross motor function (F: 8.72, *P:* 0.004). Besides this, multivariate ANOVA analysis calculated significant differences between groups with respect to the pattern of their neurological profiles favouring participants with normal neurophysiological status (F: 2.06, *P:* 0.03). With exception of differences in the outcome for the category posture, which in our opinion reflect trends in statomotor development influenced by secular acceleration, these neurological profiles may be the consequence of specific, if at all insignificant, deficits for performances in daily life procedures.

Abnormal CCT/MRI scans, defined by one or more pathological findings, were found in 50 of the 110 participants who were included in this analysis (45.5%). The most frequently observed type of CNS abnormality was cerebral atrophy (n = 42, 84%), followed by white matter disturbances (n = 16, 32%) and intracerebral calcifications (n = 3, 6%). In 18% (nine cases), cerebral atrophy was accompanied by white matter hypodensities, and in two cases (4%), calcifications and white matter alterations were combined. In the remaining 39 participants, neuroradiological investigation revealed singular types of alterations: in 33 cases (66%) cerebral atrophy, in five cases (10%) white matter hypodensities, and in one case (2%) calcifications. Intracerebral calcifications were only found in irradiated cases. Participants with disturbed EEG recordings showed a higher prevalence of morphological abnormalities (n = 25, 53.2%) compared

TABLE IV. Psychometric IQ Data for Cases With Normal and Abnormal EEG Recordings*

	Overall	EEG outcome		Statistics (F; df; *P*)
		Normal	Disturbed	
Full Scale-IQ[a]	104.7 ± 15.9	104.1 ± 16.9	105.4 ± 14.4	0.18; 1; 0.6762
Verbal-IQ	106.3 ± 15.6	105.5 ± 15.8	107.3 ± 15.4	0.35; 1; 0.5551
Information	10.0 ± 2.7	10.1 ± 2.7	10.0 ± 2.8	0.02; 1; 0.8943
Comprehension	10.9 ± 3.2	11.1 ± 3.5	10.7 ± 2.8	0.44; 1; 0.5097
Arithmetics	9.6 ± 2.8	9.7 ± 2.8	9.5 ± 2.7	0.16; 1; 0.6867
Similarities	11.3 ± 2.9	11.5 ± 3.0	11.0 ± 2.9	0.58; 1; 0.4489
Vocabulary	10.4 ± 2.9	10.5 ± 3.2	10.3 ± 2.5	0.08; 1; 0.7765
Digit span	11.2 ±3.0	10.4 ± 2.9	12.2 ± 3.4	0.14; 1; 0.2893
Performance-IQ	101.8 ± 15.9	101.4 ± 17.1	102.4 ± 2.1	0.11; 1; 0.7467
Coding	10.6 ± 2.9	10.7 ± 3.1	10.4 ± 2.7	0.23; 1; 0.6353
Picture completion	9.6 ± 3.4	9.8 ± 3.5	9.3 ± 3.2	0.56; 1; 0.4573
Picture arrangement	10.1 ± 3.2	9.6 ± 3.5	10.7 ± 2.7	3.37; 1; 0.0693
Block design	10.4 ± 3.3	10.7 ± 3.7	10.1 ± 2.8	0.82; 1; 0.3669
Object assembly	11.0 ± 2.8	10.6 ± 2.9	11.5 ± 2.6	3.11; 1; 0.0806
Kauffman factors				
VC	21.7 ± 5.4	21.9 ± 5.8	21.4 ± 4.8	0.33; 1; 0.5697
PO	20.5 ± 5.5	20.3 ± 6.1	20.9 ± 4.6	0.26; 1; 0.6133
FD	21.7 ± 5.5	21.2 ± 4.7	22.7 ± 3.5	0.75; 1; 0.3885
CFT	53.3 ± 26.2	56.3 ± 26.8	49.5 ± 25.2	1.79; 1; 0.1837
D2	52.1 ± 30.5	55.8 ± 29.7	47.1 ± 31.1	2.16; 1; 0.1451
RFT	26.6 ± 27.1	27.2 ± 27.4	25.8 ± 26.9	0.07; 1; 0.7913

*Abbreviations: VC, verbal comprehension; PO, perceptual organization; FD, freedom from distractibility; CFT, culture fair test; D2, d2 concentration and attention test; RFT, recurring figures test.
[a]Full scale, verbal and performance IQ values are expressed as standardised scores (mean: 100, S.D. 15), derived from the WISC-R/WAIS-R subtests according to the published test recommendations. CFT, D2 and RFT IQ values are expressed as percentile scores (mean: 50).

TABLE V. Interferences Between EEG and IQ Measurements*

Test	Sensitivity	Specificity	P*P*-value	N*P*-value	Likelihood
FS-IQ[a]	6.5	81.7	21.4	53.3	0.36
CFT-IQ	4.4	90.2	25.0	55.6	0.45
D2-IQ	21.7	93.4	71.4	61.3	3.29
RFT-IQ	52.2	52.5	45.3	59.3	1.09
CBCL	42.5	50.9	33.3	63.6	0.87

*Calculations based on cases with significantly disturbed EEG recordings.
[a]Abbreviations: FS-IQ, Full scale intelligence quotient based on the performance on the Wechsler intelligence scales; CFT-IQ, intelligence quotient derived from the culture fair test; D2-IQ, intelligence quotient according to the d2 concentration test; RFT-IQ, intelligence quotient derived from the recurring figures test; CBCL, child behaviour checklist; P*P*-value, positive predictive value; N*P*-value, negative predictive value.

to those without EEG disturbances (n = 25, 39.7%), but without any significance (F: 1.98; df: 1; *P:* 0.16). Morphological and neurophysiological types of abnormality were not related, either topographically or with respect to the observed severity.

DISCUSSION

The present study joins intentions of a number of reports speculating on the correlation of neurophysiological abnormalities with psychological, neurological and morphological disturbances among clinically asymptomatic long-term survivors of childhood ALL [6,7,9,22]. Primary questions were whether CNS prophylaxis with cranial irradiation prior to or during methotrexate application induced greater neurotoxicity, measured by means of EEG, than treatment regimens with radiotherapy after methotrexate or methotrexate alone, and whether the assessed EEG abnormalities are associated with signs of neurological, morphological or psychological deficits. To minimise interpretative problems that have been noted in previous studies on related topics, important factors possibly influencing our data analysis were strictly controlled: (1) children have been randomised to different procedures for CNS prophylaxis (MTX vs. MTXRT vs. RTMTX), thus reducing a potential selection bias; (2) all patients were treated according to com-

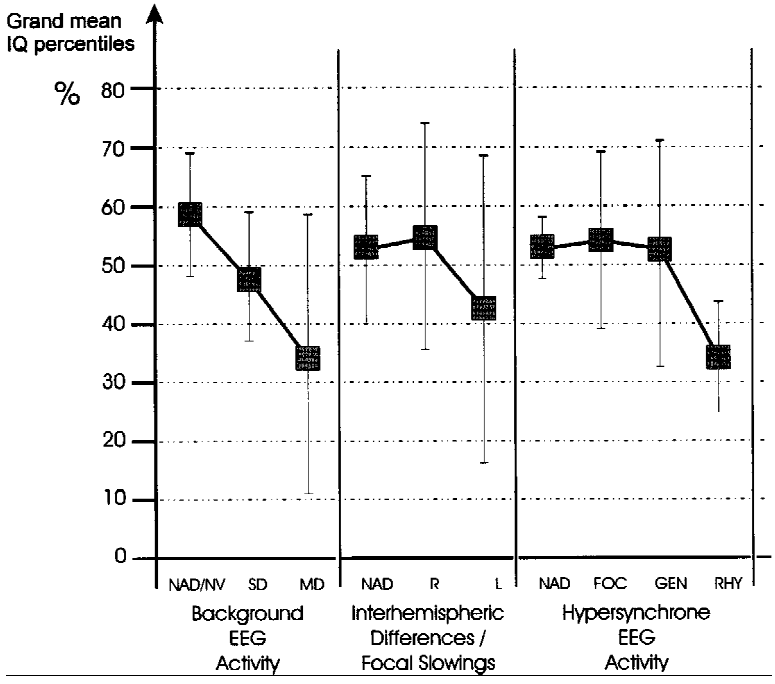

Fig. 2. Psychometric outcome in ALL long-term survivors with disturbed EEG recordings. Values shown are percent ranks (mean ± S.E. mean). Note that IQ scores decline with (a) increasing deterioration of EEG background activity, (b) presence of focal left hemispheric slowings, and (c) presence of abnormal hypersynchrone EEG rhythms. NAD/NV, inconspicious or normvariant EEG recordings; SD, slightly disturbed EEG recordings; MD, moderately disturbed EEG recordings; NAD, no EEG abnormality detected; R, right hemispheric; L, left hemispheric; FOC, focal; GEN, generalized; RHY, abnormal rhythms.

parable and highly standardised therapy protocols with the advantage of homogeneous strategies for chemo- and radiotherapy; (3) subjects involved were free of CNS involvement at the time of diagnosis; (4) showed comparable laboratory and clinical parameters; and (5) remained in first complete continuous remission after completion of therapy and until this follow-up evaluation; and (6) all investigations, performed to assess CNS function, were uniformly conducted in a highly standardised mode to prevent systemic errors.

The major result of this study is that routine EEG recordings, performed during standardised screening procedures in posttreatment surveillance studies after childhood ALL, are a worthless approach either to assess the functional or the morphological status of the human brain. There was no specific neurophysiological finding for a specific morphological substrate, neurological abnormality or psychological deficiency and vice versa. Overall, the subjects participating in this study showed an enhanced prevalence of abnormal EEG recordings without clinical evidence of CNS dysfunction. Previous studies evaluating the frequency of EEG disturbances in otherwise healthy subjects reported prevalence rates ranging between 20% [23] and 25% [24]. The main factor influencing EEG outcome was the age at diagnosis, clearly favouring subjects older than 5 years or younger than 24 months, whereas children aged 2 to 5 years at establishment of diagnosis showed an increased rate of EEG disturbances compared to all other age groups. This observation is somewhat in contrast to data of previous studies, uniformly suggesting that children who were younger (especially under 5 years of age at diagnosis) are much more vulnerable to the neurotoxic side effects of antileukemic therapy or the disease itself than children who fell ill later [25]. Our analysis, although statistically not significant, shows that younger age per se does not necessarily predispose to an increased susceptibility of the brain to the adverse effects of leukemia itself or therapy-related sequelae of CNS prophylaxis. One possible explanation for this observation may be drawn from recent studies on the development of the human brain, which were able to show that the neuronal development follows distinct stages, characterised through a dramatic increase in synaptogenesis within the first 24 months and subsequent regressive events (so-called apoptosis) with dendritic and synaptic elimination in the following years of life [26,27]. These distinct periods of neuronal metabolism have been shown to exercise important implications on the functional plasticity of the central nervous system and its susceptibility to exogenous or endogenous factors occurring during the first few years of life [28]. Our observation of a lower prevalence of disturbed EEG recordings in former ALL patients younger than 24 months of age at onset of disease might reflect the enhanced neuronal resistance in these children against methotrexate and a cranial irradiation. In contrast, chil-

TABLE VI. Psychometric Non-IQ-Related Data on Behaviour, Psychomotor Development, Concentration and Motivation (power) for Cases With and Without Significant EEG Alterations*

	Overall	EEG outcome		Statistics
		Normal	Disturbed	(F/C^2; df; *P*)
CBCL	53.3 ± 30.7	49.7 ± 31.9	58.3 ± 28.7	1.81; 1; 0.1822
Unbalanced behaviour				
before therapy (%)	28.7	32.3	23.9	0.89; 1; 0.3432
after therapy (%)	48.1	40.3	58.7	3.57; 1; 0.0588
increase (%)	67.7	25.0	145.5	
Development deficits				
before therapy (%)	2.8	1.7	4.3	0.68; 1; 0.4094
after therapy (%)	22.2	19.4	26.1	0.69; 1; 0.4053
increase (%)	700.0	1,100.0	500.0	
Lack of concentration				
before therapy (%)	10.4	11.5	8.9	0.19; 1; 0.6661
after therapy (%)	37.7	37.1	38.6	0.03; 1; 0.8719
increase (%)	263.6	228.6	325.0	
Loss of power				
frequency (%)	16.7	17.6	15.4	0.08; 1; 0.7753
Reimprovement (%)	60.0	70.0	40.0	1.25; 1; 0.2867

*Data shown represent frequencies (expressed as percent rates) for the presence of behavioural disturbances, deficits in psychomotor development, decreased concentration abilities, and loss of power. Rates are given for the life period prior to disease (i.e., before therapy), after completion of antileukemic treatment (after therapy), and as percent increase (i.e., percent ratio after/before therapy).

dren with an age of 2 to 5 years at diagnosis, passing a developmental period, characterised by (a) a rapid growth in cognitive skills and (b) a continuously decreasing neuronal plasticity, showed the highest prevalence of EEG abnormalities, reflecting their higher susceptibility to the neurotoxic side effects of leukemia and antileukemic therapy. With the progression of the CNS maturation, the discrepancy between the decreasing neuronal plasticity and the increasing CNS resistance declines continuously, resulting in continuously declining EEG disturbance rates in ALL long-term survivors older than 5 years at diagnosis. However, this hypothesis is hampered by the small number of children in the different age groups.

CONCLUSION

In conclusion, our analyses revealed an increased prevalence of EEG abnormalities in ALL long-term survivors, but we failed to corroborate results reported by other groups working on this issue: (1) with respect to EEG outcome (normal vs. abnormal) and its dependence on illness, and therapy-related parameters, respectively, statistical comparisons between the three treatment groups showed only minor and insignificant differences. According to our data, the frequency of abnormal EEGs was not influenced by the mode of antileukemic therapy. Most importantly, different types of CNS prophylaxis, either with or without cranial irradiation, did not play a relevant role with respect to the observed rate of EEG disturbances; (2) our analyses showed no significant correlation with any of the further obtained outcome measures. Subjects with abnormal EEG findings did not show higher rates of morphological or cognitive abnormalities, nor did they present with related structural disturbances or intellectual behavioural deficiencies, respectively. However, for individual cases with left hemispheric EEG abnormalities, we found a correlation between the present neurophysiological finding and an increased degree of psychological impairments.

Our data suggest that the use of conventional EEG recordings is not a useful diagnostic tool to draw conclusions on the psychological, morphological or neurological status of the subjects studied. Therefore, we conclude that routinely performed EEG recordings are of little or no value in otherwise asymptomatic long-term survivors of childhood ALL, either for the assessment of structural disturbances or for its predictive value concerning functional deficiencies. However, EEGs may be a useful tool for this purpose if: (1) additional EEG recordings prior to, during or after disease are available, which offer the opportunity to compare the development of neurophysiological parameters over time, or if (2) pre-

viously asymptomatic subjects suddenly deteriorate or present signs suggestive for cerebral seizures. In these special cases, neurophysiological procedures will be superior to other approaches to gain further and immediate insight into the functional status of the brain.

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